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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, in honor of brain tumor awareness month, it is a conversation with Dr. Jennifer Moliterno. Dr. Moliterno is an Assistant Professor of Neurosurgery and of Brain Tumor Surgery at Yale School of Medicine, and Dr. Chagpar is an Associate Professor of Surgery and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center.

Chagpar Jennifer, we do not really talk a lot about brain cancer, but it sounds really scary. First of all, can you lay the scenario for us in terms of brain cancer. There are some cancers that start somewhere else, the breast, the lung, the pancreas, that then travel to the brain, and then there are cancers that start in the brain, are those different?

Moliterno They are very different. As you were saying, there is metastatic cancer that metastasizes to the brain from another primary and then there is a cancer that originates in the brain. It is important to point out as well, there are also benign brain tumors. So anyone who hears or finds out that they have a brain tumor, it does not necessarily mean that they have brain cancer. Of course, a thorough workup needs to be done to better understand and try to characterize what type of tumor. But they do usually behave differently and of course with the metastatic tumors, you always have to take into consideration the systemic cancer. Whereas with those that originate in the brain itself, they usually do not metastasize outside of the brain, they just stay within the brain.

Chagpar Let's start at the beginning. How does one have an inkling that they may have a brain tumor? We often all get headaches, so what are the things, the symptoms that should spark us to go "oh! My gosh, I really need to seek attention."

Moliterno And after this talk, everyone will think that they have a brain tumor. Hopefully we actually lead to the opposite and people understand it a little bit more. You are right, everyone has headaches, people who have blurred vision from time to time and it may just mean that you need a new prescription for your glasses and it may just mean that you are working too hard, so the vast majority of people who have those things do not have a brain tumor. But for people who, for instance, with headaches, for people who have not had headaches and then all of a sudden they have headaches, and they are the worsening headaches, different types of headaches than their usual, that is worth

3:23 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0520-Podcast-Moliterno_333819_5_v1.mp3 getting checked out and it is worth picking up the phone and calling your primary care doctor and saying "hey, is this something I should be concerned about?" I do not think there is any harm with that. Same for visual changes. There are other tumors, usually the more aggressive types are faster growing, that might be occurring near what we call eloquent brain that has an important function, and so a tumor that is

near the motor area, for instance, someone could present with weakness. And certainly, experiencing one part of your body being weak is really not normal, and so that warrants a workup for that. There can also be tumors that occur near the speech area and so you might find subtle changes in terms of cognition or language, but again, as we are tired as the day goes on, you might kind of slur your words or stutter or something like that or forget your words. I think just looking for patterns of things happening over and over is really what should get people's attention.

Chagpar If you have this pattern, you start having headaches that you wake up with and are with you all day or you have persistent weakness in one part of your body or you have consistent changes such that you cannot grasp your words anymore, you call your primary doctor, what tests should your primary doctor be doing?

Moliterno Usually primary care doctors or even if you come to the emergency room, either one, usually they will start out with a CAT scan of the brain and they usually get that without contrast just to make sure that there is no bleed or hemorrhage or of course other types of causes for those things, stroke, etc., and so that is usually what they start with. If there is an area of concern, then usually they will follow up with an MRI, and would like to do those tests with contrast because that will better characterize the tumor. Then, when we read the MRIs and interpret it, the types of contrast enhancement, how the tumor takes up dye, that sort of thing gives us clues as to what the most likely pathology is.

Chagpar So, just based on the MRI and how the contrast is taken up by the tumor, you can get a sense of whether this is benign or malignant?

Moliterno Absolutely. What I always tell my patients is that no one knows what it is with 100% certainty. The only one who really can tell us that is the pathologist when and if we decide to take it out. But a lot of times for the more benign tumors, we do not need to take it out and we do not need to actually know what it is, and so there are a lot of different factors that go into that decision making process, but tumors look pretty characteristic and again, when you see people such as myself who do this day in and day out, we are used to looking at these things and we are used to being able to say, yeah that is what I think this is or that is what I think that is. We also have a multidisciplinary tumor board, and so if there is any concern or doubt as to what the diagnosis might be, oftentimes I will present the patient's scan at our tumor board 6:33 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0520-Podcast-Moliterno_333819_5_v1.mp3 where there are other doctors such as myself who specialize in the treatment of patients with brain tumors and we review it with our neuro- radiologist and other brain tumor doctors take a look and then we have a consensus that says "I am pretty confident that this is the diagnosis, likely benign." And if the patient is not symptomatic, oftentimes we can just follow along. If the patient is symptomatic, if the tumor is large, if there are other concerning features, then that might lead to an operation.

Chagpar So, you can get an idea whether it is benign or malignant looking at the scans, talking to your colleagues and so on, and if the patients do not have any symptoms that is great, they can live with it and you will do another scan when?

Moliterno I usually start out pretty conservatively, and

it depends, if I am concerned that there really could be malignancy and for whatever reason I am not entirely convinced of that, and I opt to repeat a scan, I may do it a little sooner, 6 weeks or so, but oftentimes if I think it is benign and I am pretty confident of that, I will usually wait about 3 months and then usually we will follow it serially over time stretching out the increments of time between scans. And as long as the person is not symptomatic, as long as the tumor is not bothering the person and the person is not bothering the tumor, they can live together and we can just follow it. But if it starts to cause problems or frankly sometimes patients just say I want it out or if it is a large size or especially if we see growth over time, then we may opt to take it out. Of course, if there is growth over a shorter period of time, that is more concerning.

Chagpar How do you tell the difference between a malignant tumor that starts in the brain versus a malignant tumor that got to the brain from somewhere else?

Moliterno It is kind of hard to be honest, and I think that there are some very subtle features, a lot of times in the way that the edema or the swelling in the brain looks, sometimes in primary brain tumors, tumors that originate in the brain, that will oftentimes be infiltrative tumor. Primary brain tumors tend to infiltrate or spread through the brain, so they do not spread outside of the brain typically, but they spread within the brain. And so, that might look a little bit different than just a tumor that came from the breast that is associated with swelling, but even so, it is often very hard to tell. Oftentimes with metastatic tumors, there will be multiple tumors and so that can be a clue as to this is coming from somewhere else. Oftentimes, those patients will have a history of cancer, and so if there is someone who was diagnosed with breast cancer, is undergoing treatment, etc., and then they present with, one other thing we did not talk about, seizures, because oftentimes patients can present with seizures, then you kind of put 2 and 2 together and you think, well they have a history of cancer, they have a mass, it probably makes that more likely, but if we ever have a question, we will get a scan of the body just to see if there is cancer elsewhere, but oftentimes the way that we manage it is very much the same. If they are symptomatic, if they are large, if the tumor is causing problems for the patient, then it really needs to come out regardless.

Chagpar So, if it is causing symptoms which presumably is why they came to you in the first place, whether it is benign, whether it is malignant, primary to the brain or whether it is metastatic, treatment is still going to involve excision?

Moliterno Oftentimes, it does. There are few tumors that even with large symptomatic tumors that we will just biopsy, meaning that we will just take a sample of the tissue and we usually do that stereotactically, meaning just with a very small delicate needle; for instance, lymphoma or certain types of cancers as well, and so, we might favor that approach in those situations because then other types of treatment are best used for those types of tumors. Of course, if there are tumors that are located in very difficult areas, areas that are really not safe to operate in, then we may opt for biopsy as well, but I try to be as aggressive as possible because there is good evidence

to support that the more tumor that is out of the head the better the patient does in the end. Chagpar But brain surgery often seems scary, at least to me and to our audience I am sure. You have got a brain tumor and now somebody is going to go in and take out a piece of your brain, how safe is that? Moliterno It is scary, I completely understand that. And when I talk to the patients, for me, in fact I just came from surgery sitting here now, for me this is what I do, day in and day out. But I do not do it to that person day in and day out and so I completely understand how scary that must be and empathize with that completely. It actually is very safe believe it or not, and especially with a couple of factors taken in. If you are seeing somebody, especially for brain tumor surgery, for instance, who is specialized in brain tumor surgery, I think that is incredibly important, research your surgeon, make sure that they really do specialize in brain tumors. Along those lines, kind of like what we have here, is to have neuro-anesthesia, to have an anesthesia team that focuses on the brain and that makes it as safe as possible. There are other types of adjuncts that we use during surgery to make it safe, and one is we have a GPS system, so that allows us to just target the tumor, and so we really do not remove brain so to speak, we remove the tumor, and so it is really taking out the bad part of the brain and leaving everything else alone. Along those lines too, we will often use what call neuro-monitoring and so with the patient asleep, we are able to monitor their motor function, some of their nerve 12:46 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0520-Podcast-Moliterno_333819_5_v1.mp3 functions. For instance, if we are working on acoustic neuromas or tumors that have to do with the hearing and balance and facial nerve, we can monitor those with the patient asleep, and sometimes, in rare situations, but sometimes, we will keep the patient awake, and that really allows us to perform a safe surgery especially when we are trying to preserve language function. Chagpar How is it that you are able to take out just the bad parts and leave the good parts if you cannot see with your naked eye the cancer cells? In other tumors we talk about taking a margin and cannot really tell where or how close you are to the cancer, there must be ways that you are able to differentiate that. We have to take a quick break for a medical minute, but when we come back, we are going to dive deeper into how exactly Dr. Moliterno and her colleagues here at Yale can take out brain cancer and still make this an incredibly safe operation. Please stay tuned to learn more about brain tumors with my guest, Dr. Jennifer Moliterno. Medical Minute Support for Yale Cancer Answers comes from AstraZeneca, a science-led biopharmaceutical company dedicated to partnering with leading scientific companies, organizations and the community to improve outcomes for advanced cancer patients. More at astrazeneca-us.com. This is a medical minute about pancreatic cancer, which represents about 3% of all cancers in the US and about 7% of cancer deaths. Clinical trials are currently being offered at federally designated comprehensive cancer centers for the treatment for advanced stage and metastatic pancreatic cancer using chemotherapy and other novel therapies. FOLFIRINOX, a combination of 5 different chemotherapies is the latest advance in the treatment of metastatic

pancreatic cancer, and research continues at centers around the world looking into targeted therapies and a recently discovered marker, hENT1. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.Chagpar This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Jennifer Moliterno. We are talking about brain tumors. Right before the break, Jennifer was talking about surgery and how here at Yale at least, when she takes out brain cancers, she is very particular to take out "just the bad stuff" and leave the rest of the brain behind, and the question I was asking Jennifer was, how exactly do you do that because in every other cancer, we cannot see tumor cells with our naked eyes, and so we talk about taking margins and wide margins in some cancers, but you really do not have that latitude in the brain?15:54 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0520-Podcast-Moliterno_333819_5_v1.mp35_v1.mp3Moliterno We are just that special in brain tumor surgery. No, you are absolutely right. And so, first to answer that question, again I think having a surgeon who is specialized in this and all joking aside, you can tell the difference to an extent, and so the area of tumor for instance, glioblastoma which is one of the types of brain cancer, one of the more malignant types of brain cancer, I can very clearly tell the difference between that and normal brain. Especially the area that takes up dye versus the rest of the brain. And we use a microscope, and it is microsurgical technique to remove it. When you start to look at the perimeter and in lower grade types of tumors especially, that is where as you said it can definitely get more blurred, and as you also said, especially if we are operating in an area of the brain that is eloquent with function, that we want to preserve, we cannot just take a huge margin, so that is where beyond our expertise, we use things like intraoperative ultrasound for one, and that gives me real-time feedback about how I am doing, the tumor will show a certain way on the ultrasound and so I will be able to tell if there is more left that does not really look like it to my eye, and then the intraoperative MRI. At Yale, we are fortunate to have a 3-Tesla intraoperative MRI, and it is the same type of MRI that the patients will have on the out-patient basis, and we have it housed in a garage in between two operating rooms, and it is on a set of tracks on the ceiling, and basically it goes back and forth between the two operating rooms to the patient. For a typical brain tumor case, I will be in there, remove the tumor, remove as much of it as I think looks like tumor based on my expertise using the ultrasound as real-time feedback, and then when I decide that it looks like I removed as much as I think, I will get an intraoperative MRI. Sometimes, there will be a little piece that is tucked up, that area that is not really the area that takes up dye but the area that extends beyond it, like the margin, which is what you are talking about and I will see can I do a little bit more with that, is that an area that is more concerning. And then, I can go back and remove that, especially if we have monitoring of the patient, it allows me to feel more comfortable in doing that.Chagpar When you talk about taking up dye, you are talking about the MRI dye, like gadolinium. And that is injected intravenously, and one

of the questions that people may have is, we can imagine that you are doing surgery and as you are doing surgery, you cut across blood vessels, how do you know that gadolinium is not going to spill, like you can still get really good images, uptake of dye. Moliterno Absolutely. It is pretty remarkable when you think about it. Chagpar Absolutely. Tell us more about other techniques that you have that are helpful to you in the operating room. This MRI is certainly beneficial as you can imagine people had an MRI before they came in and instead of relying just on the static image, you are using this in real time. 19:37 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0520-Podcast-Moliterno_333819_5_v1.mp3 Moliterno Right, and what we are able to do, for instance if there is an area of concern of tumor that remains, what we can do is, as I mentioned we usually on every case use a GPS system, and so as you said this static image, we are able to update, so now it shows the resected tumor and then it shows wherever that small amount of tumor might remain and then we can re-register it, our GPS system. And then I can literally go back in there and pinpoint exactly where it is, find it, usually yell at myself, how did I miss that, and then remove it. It only adds about half an hour to 45 minutes to the case. So, it is pretty efficiently done and really makes a huge difference. Chagpar How do patients do functionally after brain tumor surgery? Moliterno Knock on wood, it is remarkable. Patients are always so surprised, for the most part I would say my patients spend a night in the ICU and a couple of days in the hospital and they go home, and by the time they go home, they are fully functioning, they have had major surgery of course, and I always tell them to milk that as much as they can with their families, but they go home and they are fully functioning, and they are always amazed and shocked. I always do caution patients that if they come in with a deficit before surgery, and so if they come in because they have weakness and they have had weakness for some time or they have had confusion or language trouble, that oftentimes can get worse initially after surgery because of swelling and that sort of thing, but it usually will improve, but that could be a little bit of a longer course, but even so, very, very manageable with steroids and other types of salty solutions and medications that we use. Chagpar Is the primary modality for brain cancer, surgery, or do you often use chemotherapy and radiation and all of the other therapies that we throw at patients for other cancers as well? Moliterno A combination. With certain tumors such as meningiomas, acoustic neuromas, vestibular schwannomas, those primarily a lot of times it will just be surgery alone. For glioblastomas, low-grade gliomas, the more intrinsic brain tumors and the more infiltrative type of brain tumors, I always say that this is not just a surgical disease, surgery helps debulk and certainly the more the tumor that is removed the better, because of course in theory, the less that the radiation and the chemotherapy needs to work on. But it is not a purely surgical disease, there is usually some other type of therapy that they need and usually it is radiation and chemotherapy. Here at Yale, we sequence every brain tumor, meaning that we look at the genetics underlying every brain tumor that comes through, and so that allows us to see the patients who might be eligible for certain clinical trials, it might also

allow us to take a more precise or personalized approach to treatment too.22:54 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0520-Podcast-Moliterno_333819_5_v1.mp3Chagpar Tell us more about the clinical trials ongoing in brain cancer because we often talk on the show about clinical trials and the value that they have in terms of people who participate in clinical trials tend to do better than people who do not, they are really getting kind of tomorrow's therapies today, so what are tomorrow's therapies, what are the exciting advances in clinical trials in brain cancer at the moment?Moliterno Some of them are very similar to other types of cancer in the body -- immunotherapy or small molecule inhibitors, that sort of thing. There is one study actually that I am principal investigator on here that allows us to inject a virus at the time of surgery into the resection cavity, so after I remove the tumor, I am able to inject this virus which then will turn basically an antifungal drug, a very well-tolerated drug into a chemotherapy. So, that is pretty exciting as well, and they have shown some pretty nice results. I would say that with these types of brain tumors, particularly glioblastoma which is the most malignant and aggressive type, they are very heterogenous, meaning that they do not all fit into the same way of treatment, they are not all going to respond the same. And so, I think kind of coming at it and trying to be as thoughtful, particularly they are from a molecular basis as possible is probably the best strategy and that certainly what we try here.Chagpar But when we think about molecular strategies, I mean oftentimes at least in other tumor types, we are thinking about looking at what particular mutation a tumor might have and then targeting it with a drug, and the drugs are often given intravenously, the question that I think a lot of people may have with regard to brain cancers, however, is that you have got this thing called the blood brain barrier, tell us more about that and whether it is problematic or not?Moliterno It can be problematic, it really can be. I think that that is one of the reasons why it has been so difficult to treat brain tumors. As I always say, these tumors are very, very challenging, these particular tumors. Of course, again, there are other types such as meningiomas, acoustic neuromas, etc., I do not want to kind of scare everybody who hears brain tumors and you cannot really treat one as the next, they really are dependent on the type that they are. But if we are talking about the more malignant, more aggressive types, they are very difficult to treat, and for those reasons as you said, one of them as we discussed already, is that the brain is important and even quiet parts of the brain are still important and so you cannot get that huge wide margin as you wish. Sometimes we can, but sometimes it can be a lot more challenging for sure and that is why we try to be as aggressive, at least I do here at Yale, as possible with removing as much tumor as possible and safely. The blood brain barrier, along those lines, the response of the brain to the medications and to radiation, and so radiation certainly helps with these tumors, but it can also cause swelling, and so then we are 26:09 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0520-Podcast-Moliterno_333819_5_v1.mp3kind of battling against that with steroids and other types of things to deal with that, which sometimes can

have issues with wound healing and it really does become a balance. Chagpar In terms of prognosis, when we think about primary brain cancers, the more malignant primary brain cancers, if the patients come in and they have this resected, what is their prognosis? Moliterno That is really the first question that the patient always wants to know and the family wants to know, especially when I meet with the family in the waiting room, that is what they want to know, and of course, it really does vary. It varies on the type of tumor, it varies on the make-up of the type of tumor and that is why it is so important to understand molecular make-up. There are certain types of profiles that correlate with a better prognosis versus a worse prognosis. I would say again, referring to glioblastoma, and more aggressive types of brain tumors, they usually can be kept at bay for a certain amount of time, but they are pretty smart tumors and again they are very heterogeneous and so they know how to mutate and outsmart the chemotherapy and the radiation, and so ultimately it is more a question of when they recur rather than if, and when that happens, then we kind of start back at the drawing board and think, is surgery a possibility, is more radiation a possibility, usually we limit that to one time, but sometimes we do more. And then, changing the chemotherapy to something different, changing a clinical trial, etc. Chagpar So, surgery for a recurrence is a possibility? Moliterno Absolutely. We try to be very aggressive with that and the benefits of that as well is to understand the changes in the tumors too from a genetic standpoint and see if maybe, as you said, is there something that we can target a little bit different, what changed in terms of the profile and we really see that actually at our tumor board because we have a precision tumor board, which looks at just that and we will review the mutations for all the tumors that come through and then we will say, did something change, is there another way that we could be more creative and target this and try to keep it at bay longer, and we have had a lot of success with that. Chagpar We have not talked a lot about the brain tumors that are metastatic from other sites. So, in one minute, can you just tell us, are those things that you would routinely resect or are these more a manifestation of systemic disease? 29:02 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0520-Podcast-Moliterno_333819_5_v1.mp3 Moliterno I think it really depends on several things. I think it depends on the type of tumor that it is. It depends whether there is one or multiple. It depends whether or not the patient is symptomatic or not. And it depends whether or not it is radiosensitive. And so, that is another modality for treating particularly metastatic cancer. Dr. Jennifer Moliterno is an Assistant Professor of Neurosurgery and of Brain Tumor Surgery at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.